Anticoagulation management after a clot

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University of Warwick
What this presentation covers

• Background
• Current treatment
• New agents
• Duration of treatment
“Of course what really scares me is the deep vein thrombosis risk”
VTE risk
Aims of treatment

• To prevent extension
• To prevent embolisation
• To allow stabilisation and recanalisation
• To prevent recurrence
• To prevent long term effects (PTS, PH)
Current Treatment

• Initial treatment with UFH, LMWH, SP
• No placebo controlled trials
• Minimum 5 days (average 7)
• LMWH drug of choice for cancer patients
Current Treatment

- Combined with warfarin (VKA)
- Treatment phase 3-12 months
- One placebo controlled trial (PE pts, Barritt and Jordan 1960)
- Duration of therapy?
Current Treatment – What’s the problem?

- INR monitoring
- Which LMWH – HIT??
- Bleeding versus recurrence
- Duration of therapy
Einstein

....not him
**Rivaroxaban EINSTEIN phase III: study designs**

**EINSTEIN DVT**¹ and **EINSTEIN PE**² (non-inferiority studies)

Treatment period of 3, 6 or 12 months

- **Confirmed acute symptomatic DVT without symptomatic PE**
  - N=3,449
  - Rivaroxaban 15 mg bid
- **Confirmed acute symptomatic PE with or without symptomatic DVT**
  - N=4,833
  - Enoxaparin 1.0 mg/kg bid for at least 5 days, followed by VKA to start ≤48 hours, target INR range 2.0–3.0
  - Day 1
  - Day 21

**EINSTEIN Extension**¹ (superiority study)

Treatment period of 6 or 12 months

- **Confirmed symptomatic DVT or PE completing 6 or 12 months of rivaroxaban or VKA**
  - N=1,197
  - Rivaroxaban 20 mg od
  - Placebo
  - Day 1

30-day observation after treatment cessation

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L.GB.01.2013.1379 Jan 2013
Einstein DVT- results

- 3449 pts (1731 Rivaroxaban)
- Rivaroxaban 36 (2.1%) vs 51 (3%) recurrent events
- Major bleeding 8.1% in both
Einstein PE

As per DVT study
4,833 pts
Non-inferior
L.GB.01.2013.1379 Jan 2013
Einstein - Conclusion

Rivaroxaban

• Non-inferior acutely compared with standard therapy
• Superior in terms of secondary prevention compared with placebo but some excess bleeding
• Pre-specified joint analysis suggest superiority of rivaroxaban
Einstein

A new era?
## NOAC VTE trials

<table>
<thead>
<tr>
<th>DRUG</th>
<th>TRIAL</th>
<th>INITIATION</th>
<th>MAINTAINANCE*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DABIGATRAN</td>
<td>RE-COVER</td>
<td>LMWH ≥ 5 days</td>
<td>150mg bd</td>
</tr>
<tr>
<td>RIVAROXABAN</td>
<td>EINSTEIN</td>
<td>15mg bd 21 days</td>
<td>20mg od</td>
</tr>
<tr>
<td>APIXABAN</td>
<td>AMPLIFY</td>
<td>10mg bd 7 days</td>
<td>5mg bd</td>
</tr>
<tr>
<td>EDOXABAN</td>
<td>Hokusai-VTE</td>
<td>LMWH ≥ 5 days</td>
<td>60mg od</td>
</tr>
</tbody>
</table>

* GFR>50 ml/min
Length of Treatment

• 1st episode of idiopathic VTE should be treated with warfarin at an INR of 2.0 to 3.0 at least three months

• the optimal length of time and optimal degree of anticoagulation are not known

• Baglin T et al. JTH 2012 Duration of anticoagulant therapy after a first episode of unprovoked pulmonary embolus or deep vein thrombosis: guidance from the scientific and standardization committee of the international society on thrombosis and haemostasis.

• Boutitie F et al. BMJ 2011; 342:d3036 Influence of preceding length of anticoagulant treatment and initial presentation of venous thromboembolism on risk of recurrence after stopping treatment: analysis of individual participants' data from seven trials.
Risk of recurrent VTE based on history of index event

Risk of recurrence after unprovoked VTE 30-40% after 5-10 years

Cambridge cohort
Baglin et al Lancet 2003; 362: 523–26
Length of Treatment – balance of risks
Thrombosis vs bleeding

• Risk benefit analysis
• Patients values and preferences in regard to such risks and benefits
• The potential benefit of extending anticoagulation to six (or more) months may be offset by a higher risk of bleeding and the greater cost and inconvenience of the longer duration of treatment
2012 ACCP Guidelines

Recommendations based upon the perceived balance between

• the number of deaths from recurrent VTE prevented by continued anticoagulation versus

• the number of fatal bleeding episodes associated with continued anticoagulation
## Risk of rVTE after discontinuation of anticoagulation

<table>
<thead>
<tr>
<th>Risk or rVTE</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; year</th>
<th>Thereafter</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; VTE provoked by surgery</td>
<td>1%</td>
<td>0.5%</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; VTE provoked by a nonsurgical factor</td>
<td>5%</td>
<td>2.5%</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; unprovoked VTE</td>
<td>10%</td>
<td>5%</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; episode unprovoked VTE</td>
<td>15%</td>
<td>7.5%</td>
</tr>
</tbody>
</table>
## Risk of major bleeding if anticoagulation is continued

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Risk category</th>
<th>During 1st 3 months</th>
<th>Thereafter/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>LOW</td>
<td>1.9%</td>
<td>0.9%</td>
</tr>
<tr>
<td>1</td>
<td>INTERMEDIATE</td>
<td>3.2%</td>
<td>1.6%</td>
</tr>
<tr>
<td>➤ 2</td>
<td>HIGH</td>
<td>12.8%</td>
<td>&gt; 6.5%</td>
</tr>
</tbody>
</table>
BLEEDING

- Warfarin in top 10 drugs largest number of serious adverse event reports submitted to the United FDA
- Anticoagulants also ranked first in 2003 and 2004 in the number of total mentions of death for drugs "causing adverse effects in therapeutic use"
- a common cause of emergency department visits
- "black box" warning re warfarin's bleeding risk
- Related to the degree of anticoagulation as well as the presence in the patient of pre-existing risk factors for bleeding.
<table>
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<tr>
<th>Thrombotic recurrence risk group</th>
<th>LOW bleeding risk group</th>
<th>INTERMEDIATE bleeding risk group</th>
<th>HIGH bleeding risk group</th>
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</thead>
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<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; VTE provoked by surgery</td>
<td>Discontinue (strong)</td>
<td>Discontinue (strong)</td>
<td>Discontinue (strong)</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; VTE provoked by a nonsurgical factor or 1&lt;sup&gt;st&lt;/sup&gt; unprovoked distal DVT</td>
<td>Discontinue (weak)</td>
<td>Discontinue (weak)</td>
<td>Discontinue (strong)</td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; unprovoked proximal DVT or PE</td>
<td>Continue (weak)</td>
<td>Continue (weak)</td>
<td>Discontinue (strong)</td>
</tr>
<tr>
<td>2&lt;sup&gt;nd&lt;/sup&gt; episode unprovoked VTE</td>
<td>Continue (strong)</td>
<td>Continue (weak)</td>
<td>Discontinue (weak)</td>
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ISTH guidance 2012 – unprovoked VTE

- In favour of long term a/c (>3-6 months)
  - Male
  - Moderate to severe PTS
  - Ongoing dyspnoea
  - Satisfactory a/c control
  - Elevated D-dimer 3-4 weeks after stopping (using study validated assay)
Issues to consider

• Patient information and counselling
  – Estimated risk of recurrence
  – Bleeding risk
  – Patient values and preferences

Age, comorbidities, quality of life issues
Amplify-Ext: Apixaban for VTE

<table>
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<th>Apixaban 5mg bd</th>
<th>Placebo</th>
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<td>Recurrent VTE</td>
<td>1.7%</td>
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<td>8.8%</td>
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<td>Non-major bleeding</td>
<td>3.2%</td>
<td>4.3%</td>
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Symptomatic VTE or death

n = 829
n = 840
n = 813

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Major or Clinically Relevant Non-major Bleeding

Length of Treatment

Who is truly low risk of recurrence?

Who is truly high risk of bleeding?
Other issues

- Stockings
- HRT/OCP
- Aspirin
- Travel
- Hospital Admission
Conclusion

• New agents now available
• Optimal length of time of anticoagulation are not known (low risk of recurrence)
• Cost?
• New care pathways
• Warfarin here for a while yet